Remarks

In response to the Final Office Action mailed 20 March 2007 the applicant herein submits the following amendments and remarks.

The applicant provides the following submissions with this communication: 1) applicant's facsimile cover page; 2) Transmittal Form (PTO/SB/21), 3) Certificate of Transmission (PTO/SB/97); 4) Petition for 3 Month Extension of Time under 37 C.F.R. §1.136(a) (PTO/SB/22); 5) a Request for Continued Examination (R.C.E.) under 37 C.F.R. §1.114 (PTO/SB/30); and 6) the applicant's substantive Amendment and Response (29 pages).

The Final Office Action set a three-month Shortened Statutory Period 20 June 2007 extendable under 37 C.F.R. §1.136(a) for submission of a responsive communication. Applicant's response is thus timely filed in view of the Petition for extension and payment of extension fee pursuant to 37 C.F.R. §1.17(a)(3). The applicant authorizes the Commissioner to charge, or credit any overpayment, associated/necessary with this communication to U.S.P.T.O. Deposit Account No.: 50-0244.

Claims 18-36, 46, 48-51, 56 and 57 are currently pending. The applicant has amended claims 18, 19, 22, 29, and 35 in order to advance prosecution and his business interests, without acquiescing to the Examiner's arguments and reserves the right to prosecute claims directed to any canceled or amended subject matter in the future. The claim amendments are fully supported by the specification as originally filed and do not add new matter. Furthermore, the applicants Request for Continued Examination provides the opportunity to amend to claims.

The applicant's Amendment and Response mailed 18 December 2006 rendered the following previously made rejections moot:

1. The rejection of claims 52 and 54 as containing new matter (Final Office Action ¶ 6);
2. The rejection of claims 52 and 54 as being obvious (Final Office Action ¶ 7); and
3. The rejection of claims 52 and 54 as being indefinite (Final Office Action ¶ 8).

The Examiner withdrew the following previously made rejections in the Final Office Action mailed 20 March 2007:

1. The rejection of claim 26 under 35 U.S.C. §112, ¶ 2, as being indefinite (Final Office Action ¶ 9);
2. The rejection of claims 49 and 50 as being indefinite (Final Office Action ¶ 10);
3. The rejection claim 48 as being indefinite (Final Office Action ¶ 11);

4. The rejection of Claim 49 under 35 U.S.C. §112, ¶ 1, as containing new matter (Final Office Action ¶ 12);
5. The rejection of claims 46 and 48 as containing new matter (Final Office Action ¶ 13);
6. The rejection of claim 18 as being indefinite (Final Office Action ¶ 14);
7. The rejection of claim 22 as being indefinite (Final Office Action ¶ 15);
8. The rejection of claim 35 as being indefinite (Final Office Action ¶ 16);
9. The rejection of claim 23 as being indefinite (Final Office Action ¶ 17);
10. The rejection of claims 24, 25, 27-29, and 33 as being indefinite (Final Office Action ¶ 18);
11. The rejection of claims 30-32 as being indefinite (Final Office Action ¶ 19);
12. The rejection of claim 35 as being indefinite (Final Office Action ¶ 20);
13. The rejection of claim 51 as being indefinite (Final Office Action ¶ 21);
14. The rejection of claim 57 as being indefinite (Final Office Action ¶ 22);
15. The rejection of claims 46 and 48 as being indefinite (Final Office Action ¶ 23); and
16. The rejection of claims 19-29-33-35-46, 48-51, 56, and 57 as being indefinite (Final Office Action ¶ 24).

All pending claims currently stand rejected in the Final Office Action mailed 20 March 2007 as follows:

1. The amendment to the Specification is objected to under 35 U.S.C. §132 as introducing new subject matter (Final Office Action ¶ 5);
2. Claim 19 stands rejected under 35 U.S.C. §112, ¶ 2, as being indefinite (Final Office Action ¶ 25);
3. Claims 18-33 and 51 stand rejected under 35 U.S.C. §103(a) as being obvious over McMaster (U.S. 6,146,902) in view Andre *et al.* (In: Modern Vaccinology, (Ed) Kurstak et al. Plenum Medical Book Company, New York, NY, *pp.* 41-54, (1994)), Levine *et al.* (In: Abstracts of the Tenth International Pathogenic *Neisseria* Conference, (Ed) Zollinger et al. Baltimore, MD, *pp.* 228-230 (1997)), and Lindberg (Vaccine, 17:S28-S36 (1999)) (Final Office Action ¶ 26);
4. Claims 18-36, 46, 48-51, 56,and 57 stand rejected under 35 U.S.C. §103(a) as being obvious over Costantino *et al.*, (Vaccine, 10:691-698 (1992)) and McMaster in view of Andre *et al.*, Levine *et al.*, and Lindberg (Final Office Action ¶ 27);
5. Claim 35 stands rejected under 35 U.S.C. §112, ¶ 1, as containing new subject matter (Final Office Action ¶ 28);
6. Claim 29 stands rejected under 35 U.S.C. §112, ¶ 2, as being indefinite (Final Office Action ¶ 29);
7. Claims 30-32 and 36 stand rejected under 35 U.S.C. §112, ¶ 2, as being indefinite (Final Office Action ¶ 30);
8. Claim 35 stands rejected under 35 U.S.C. §112, ¶ 2, as being indefinite (Final Office Action ¶ 31);
9. Claims 22-25 stand rejected under 35 U.S.C. §112, ¶ 2, as being indefinite (Final Office Action ¶ 32); and
10. Claim 35 is objected to for reciting brackets therein (Final Office Action ¶ 33).

In the following remarks, the applicant will refer to the forgoing rejections numerically as referenced above. The applicant has grouped like rejections for clarity and efficiency.

The amendments and remarks submitted herein are intended: 1) to be responsive; 2) to advance the prosecution of the present application; and 3) to place the application in condition for immediate allowance. Accordingly, reexamination and reconsideration of the claims is respectfully requested.

Rejections 1 and 5: The New Subject Matter Objections to the Specification and to Claim 35

In the 3 October 2005 Office Action the Examiner objected to the proposed amendment to the specification submitted by in his 7 June 2005 communication. The Examiner refused to enter the proposed amendment. The applicant withdraws the proposed amendment without prejudice. The objection to the specification is thus moot.

The examiner also rejected claim 35 as allegedly containing new matter. In the Final Office Action, the Examiner states:

> First, the limitations mentioned above by Applicant, i.e., '(N-2-Deoxy-2-L-leucylamino hydroacetate' and '(3-cholesterol)' do not appear in the claim. Instead, the limitations '(N-2-Deoxy-2-L-leucylamino-β-D-glucopyranosyl)-*N*-octadecyldodecanoylamide hydroacetate' and '(3-β-[N-(N',N'-demethylaminoethane)-carbamoyl] cholesterol)' are included in the claim. Second, the introduction of the brackets appears to exclude what is recited within the brackets. Third, the instant specification, as filed, does not provide support for these expanded limitations.

(Final Office Action, ¶ 28). The Examiner's concerns are moot in view of the above-described amendment to pending claim 35.

Rejections 2, 6, 7, 8, and 9: The Indefiniteness Rejections

Claims 19, 29, 30-32, 35, 36, and 22-25 stand rejected as being indefinite. The indefiniteness rejections are addressed in the order in which they were presented.

Claim 19 was rejected as being indefinite in ¶ 25 of the Final Office Action. The applicant has addressed the Examiner's concerns. Accordingly, this rejection should be withdrawn.

Claim 29 was also rejected as being indefinite in ¶ 29 of the Final Office Action. The applicant has addressed the Examiner's concerns. Accordingly, this rejection should be withdrawn.

Claims 30-32 and 36 were also rejected as being indefinite in ¶ 30 of the Final Office Action based upon the alleged indefiniteness of base claim 18. The previous indefiniteness rejection of claim 18, recited in the 3 October 2005 Office Action at ¶ 53(a), contained a request from the Examiner that applicant insert the phrase "capsular polysaccharide from *N. meningitidis* of serogroup A, C, W-135, or Y" into the claim. The applicant complied with the Examiner's request in his 3 April 2006 communication. The applicant thus believes the Examiner's indefiniteness concerns regarding these claims have been addressed.

The indefiniteness rejection of claim 35 set forth in ¶ 31 of the Final Office Action is moot in view of the above-mentioned amendments to the claim.

Claims 22-25 are allegedly indefinite as set forth at ¶¶ 32(a), (b), and (c) of the Final Office Action. The rejection of claim 22-25 is moot in view of the above-mentioned amendments made to claim 22.

The applicant is grateful for the Examiner's suggestions to overcome the indefiniteness rejections. The applicant respectfully requests that these rejections be withdrawn.

Rejections: 3 and 4 The Obviousness Rejections

All of the originally filed claims stand rejected as being obvious under various combinations of references.

Specifically, claims 18-33 and 51 are rejected under McMaster (1998) in view Andre *et al.* (1994), Levine *et al.* (1997), and Lindberg (1999). (Final Office Action, ¶ 26). Claims 18-36, 46, 48-51, 56, and 57 are rejected under Costantino *et al.*, and McMaster in view of Andre *et al.*, Levine *et al.*, and Lindberg. (Final Office Action, ¶ 27). For the following reasons, the rejections of the claims are traversed and should be withdrawn.

The factual inquires set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), set out the framework for applying the statutory language of §103: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) considering

any relevant secondary considerations. The U.S. Supreme Court's recent *KSR v. Teleflex* decision did nothing to undermine or diminish the importance of this landmark case in patent law. (*KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (U.S. Apr. 30, 2007)).

Nor did the *KSR v. Teleflex* decision strike down the well settled teaching, suggestion, motivation to combine ("TSM") test promulgated by the Federal Circuit as an important component of obviousness examination.[1] Indeed, the U.S. Supreme Court specifically held that the "TSM" test provides a "helpful insight" when assessing obviousness. What the Court cautioned against were rigid and formulaic applications of the TSM test by the Federal Circuit to reach results that otherwise contravene common sense especially when handing down decision in predictable fields of endeavor.

It is important to note that the Court's decision was based on facts arising from a simple and predictable mechanical art. In fact, the Court found that the level of skill in the pertinent art was that of an undergraduate degree in mechanical engineering or an equivalent level of industry experience (*i.e.*, any working knowledge of simple levers and pivots, and stock sensors components) in the automotive industry. (*KSR, p.* 8) The technology at issue in the *KSR* decision involved the combination of known and tangible components functioning in their usual and customary ways in the mechanical art which are recognized as inherently predictable. The Supreme Court did not reach its decision upon consideration of facts and issues arising from an unpredictable field.

Nonetheless, even in predictable fields when working with known elements the Supreme Court cautioned that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." (*KSR, p.* 14). Thus, the focus of *KSR* can be summarized by saying the predictability, and conversely the unpredictability, in a given field of inventive endeavor must always be weighed in every obviousness determination.

[1] The TSM test components/criteria are as follows. There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. (MPEP § 2143.01). Second, there must be a reasonable expectation of success. (MPEP § 2143.02). Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (MPEP § 2143.03).

The Examiner summarizes the applicant's previous arguments and then summarily states that "The Office has clearly set forth a *prima facie* case of obviousness. No obvious to try rationale has been used." (Final Office Action, ¶ 27, *p.* 9, *ll.* 6-7). The Examiner next asserts support for the obviousness rejections by primarily discussing the Granoff (WO 98/58670), McMaster, Levine *et al.* and Lindberg references.

The applicant will first turn to the Examiner's discussion of Granoff. In the 7 January 2004 Office Action at ¶ 16, the Examiner set forth an obviousness rejection of claims 18-33, in pertinent part, over Granoff.[2] In due course, the applicant submitted that Granoff contained conspicuous and significant omissions that precluded its combination with the other cited references. In view of the applicant's remarks, the Examiner withdrew the rejection in the 7 December 2004 Office Action at ¶ 13. In the very next Office Action, mailed 3 October 2005, the Examiner reiterated that rejection over Granoff had been withdrawn. (3 October 2005 Office Action, ¶ 47). Indeed, none of the last three Office Actions contained a formal rejection over Granoff in combination with any other reference. Applicant objects to the rejection of the claims in view of Granoff based on the Examiner's prior withdrawal of Granoff. Applicant believes it is improper to raise a ground of rejection previously withdrawn, particularly in the context of a final rejection.

The above remarks notwithstanding, the applicant is again obliged to briefly discuss the Granoff reference. First, the Examiner's argument that Granoff did not *deter* McMaster and Levine is inapposite. The applicant respectfully submits that *prima facie* obviousness is concerned with what a reference allegedly teaches or suggests to others to do. The fact that Granoff does not allegedly contradict McMaster and Levine *et al.*, does not in any way enhance the Examiner's argument. It is easy to imagine that a reference could be used in innumerable ways if the Examiner's were permitted to merely declare what reference does not deter one from doing. Second, in the present case, given prevailing *meningococcal* serotype distribution and disease occurrence when Granoff was published, the reference's omission of Y and W-135 serogroups from any combination disclosed therein is conspicuous and significant. Granoff's failure to include these important serotypes in the combinations discussed therein is conspicuous and significant given Granoff's reputation and stature within the vaccine

community. The applicant has consistently submitted this point in previous communications to the Office to which the Examiner has acquiesced.

The applicant next discusses the Lindberg paper. The Lindberg paper is devoid of data concerning any glycoconjugate. It does not teach or suggest with the required specificity how to make and use any composition pertaining to *N. meningitides* serogroups of A, C, Y, and W-135. It should be viewed as a topical review of the field generally. It was published in a special review edition of the subject journal. It does not contain the requisite evidentiary support necessary to serve as a component of a *prima facie* obviousness rejection. The applicant pointed out many of these shortcomings already. At best, Lindberg provides hope for the eventual development of a multivalent meningococcal vaccine.

Contrary to the Examiner's assertions concerning *N. meningitides* B-serotype polysaccharide-protein conjugates, the Lindberg paper teaches that B-serotype conjugates were an unfulfilled promise. Lindberg's statements are an invitation to try which is analogous to the impermissible obvious to try rationale. To illustrate, Lindberg devotes an entire section (*i.e.*, § 4.2) to describing the difficulties in making a *N. meningitides* serotype B conjugates. It was well know in the art that the B-serotype polysaccharide is poorly immunogenic in humans due to humans' innate immunological tolerance for the B serotype polysaccharide. This tolerance is due to the structural similarity of the polysaccharide to an embryonic neural cell adhesion molecule. Nevertheless, Dr. Lindberg maintains that there is the promise of an efficacious *N. meningitides* serotype B polysaccharide-protein conjugate. (Lindberg, S34, §4.2, entire paragraph). To date, there remains no widely efficacious B-serotype vaccine.

Lindberg recognizes the unpredictability of the vaccine art. For example, §2.4 of the Lindberg paper describes one genetic basis for vaccine failure. This is an example of art recognized unpredictability in the field of vaccinology. Dr. Lindberg states "Although the use of glycoconjugate vaccines may overcome some of the allotype associations with T-cell independent responses to polysaccharide vaccines, *it may not be the panacea we hoped for.*" (Lindberg, S31, §2.4, ¶ 4, emphasis added). Similarly, § 3.2 of the paper speaks of other potential genetic based hurdles to overcome in the production of efficacious polysaccharide-

[2] Claims 18-33 were rejected as allegedly being obvious under 35 U.S.C. §103(a) over Granoff (WO 98/58670) in view Ambrosh *et al.*, (Bull. WHO 61(2):317-323 (1983)) and Andre *et al.*

protein conjugate vaccines. These statements cast doubt on the prospects for successfully producing glycoconjugate vaccines.

Furthermore, Dr. Lindberg predicted the development the of a "pneumococcal conjugate vaccine [that] will contain from 9 to 11 different polysaccharides." (Lindberg, S32, §3.1, ¶ 5). The Wyeth Pharmaceuticals, Inc., PREVNAR® heptavalent (*i.e.*, 7 serotypes) pneumococcal-polysaccharide-protein conjugate vaccine remains the only licensed polysaccharide-protein conjugate pneumococcal vaccine.

In the paragraph immediately preceding that relied upon by the Examiner as a basis for her arguments concerning the Lindberg's paper, Dr. Lindberg himself speaks of a SURPRISING and UNEXPECTED failure of a *N. meningitides* A-serotype polysaccharide-protein conjugate to induce immunological memory (a hallmark of a successful polysaccharide-protein conjugate vaccine). (Lindberg, S34, §4.1, ¶ 4). Dr. Lindberg summarizes the failure described in the 1997 paper by Leach *et al.* (Leach *et al.*, *Induction of immunological memory in Gambian children by vaccination in infancy with a group A plus C meningococcal polysaccharide-protein conjugate vaccine*, J. Infect. Dis., 175:200-204 (1997)). (Appendix 1). Notably, the BIVALENT serotypes A and C conjugates administered concomitantly failed to produce the hoped for results. The Leach *et al.* paper provides further evidence that polysaccharide-protein conjugate vaccines are unpredictable even in cases of as few as two known glycoconjugates being concomitantly administered.

As a final example of Dr. Lindberg's hopeful predictions, in §5 of the paper, Dr. Lindberg opines that successful polysaccharide-protein conjugate vaccines will be developed against: 1) group B *streptococci*; 2) *Salmonella typhi* Vi polysaccharide; and the capsular and lipopolysaccharide of 3) *Escherichia coli*; 4) *Shigella sonnei*; and 5) *S. Flexneri*. To the applicant's knowledge, no such efficacious polysaccharide-protein conjugate vaccines exist. This highlights the somewhat hyperbolic nature of the paper and the unpredictability in the field of vaccinology.

The Examiner is respectfully reminded that each reference must be considered for all that it teaches or suggests not just that which is the most favorable to the asserted position. In view of the forgoing, it is clear as a whole that the Lindberg reference is merely a collection of desires for effective vaccines that have largely eluded those of skill in the art.

The applicant now turns to Levine *et al.* The Examiner cites Levine apparent as providing additional evidence of the feasibility of an A, C, Y, W-135 glycoconjugate vaccine. In particular, the Examiner states:

> Because a reasonable expectation of success of such a combined conjugate vaccine was anticipated by those of skill in the art at the time of the invention, Levine *et al* went to the extent of performing a cost effectiveness analysis for routine immunization with a quadrivalent A,C, Y and W-135 meningicoccal polysaccharide-protein conjugate vaccine. These are clearly indicative of a reasonable expectation of success with a combination meningococcal A+C+Y+W-135 glyconjugate vaccine.

(Final Ofice Action, ¶27). Interestingly, the Examiner states Levine *et al.* provides a "cost-effectiveness analysis for routine immunization" with a tetravalent A, C, Y and W-135 polysaccharide-protein conjugate vaccine. (Final Office Action, ¶27).

Levine is replete with baseless suppositions regarding the nature of future vaccine modeled therein. The self-described "**key estimates**" mentioned in Levine *et al.* have previously been discussed. (Levine *et al.*, *p.* 228, ¶ 2, emphasis added). Levine *et al.* state "The C-E of MenConj vaccine in this analysis **depends** on some **important assumptions**. First, it must be administered in the same syringe with the Hib conjugate vaccine (or other appropriate vaccine)." (Levine *et al.*, *p.* 229, ¶ 5, emphasis added). Levine *et al.* fail to provide any suggestion of how to achieve this hypothetical vaccine. In the absence of a full and complete explanation of the justification in the Examiner's acceptance of Levine's conclusions—which are admittedly are based on **key estimates** and **important assumptions**—the probative value of Levine *et al.* as part of the present combination of references is dubious.

The applicant further submits that Levine *et al.* provide no probative support in relation to the reasonable expectation of success. The reasonable expectation of success is a reasonable likelihood of TECHNICAL success, not economic success. While suggestions of economic success can motivate a potential inventor to work hard, the promise of financial reward does not confer the inventor with any particular increased level of insight into achieving a solution to a problem. At best, the paper points to perhaps the obviousness of trying to make cost-effective *N. meningitides* serotype vaccines.

The fact that an economic analysis was performed on a non-existent therapeutic is of no consequence. Extending the Examiner's rationale in applying Levine *et al.*, one could draft a

paper arguing that a cancer vaccine or perhaps an AIDS vaccine would certainly also be cost-effective and beneficial as compared to the wrath of these diseases and their costs on society thereby rendering such vaccines obvious.

In fact, such papers regarding the modeling of the cost-effectiveness of a prostate cancer chemotherapeutic and of an AIDS vaccine exist. (*See, Svatek et al., The cost of prostate cancer chemoprevention: a decision analysis model*, Can. Epidemiol. Biomarkers Prev, 15(8):1485-1489 (2006) [Appendix 2]; and *Bishai et al., Modeling the economic benefits of an AIDS vaccine, Vaccine*, 20:526-531 (2001) [Appendix 3]). Five years after Bishai *et al.*, we remain waiting for the AIDS vaccine Bishai *et al.*, modeled. Additionally, Scott *et al.*, performed an cost-benefit analysis concerning the use of meningococcal vaccines in college freshmen and came to the conclusion that it was not a cost effective to use meningococcal vaccines despite the disease prevention that would be obtained. (*See*, Scott *et al., Vaccinating First –Year college Students Living in Dormitories for Meningococcal Disease*, Am. J. Prev. Med. 23(2):98-105 (2002) [Appendix 4]). Despite this analysis, the Center for Disease Control, Advisory Committee on Immunization Practices, and the American Academy of Pediatrics as well as most universities have strongly urged the use of the MENACTRA® vaccine in this population. The Scott *et al.* reference teaches away from continuing efforts to develop meningococcal vaccines as are presently claimed. The applicant submits that none of these aforementioned papers are of any value in actually guiding one skilled in the art in developing the desired therapeutic agents.

Finally, given Levine *et al.* is advanced as providing a cost-effectiveness analysis of multi-serotype vaccine compositions to combat invasive meningococcal disease, it is interesting that the authors do not once even mention or consider the potential cost-effectiveness and societal benefits of a *N. meningitides* **B-serotype** polysaccharide conjugate vaccine. The B-serotype remains a public health issue. This is especially interesting given the Examiner's arguments concerning B-serotype polysaccharide protein conjugates and the alleged motivation to conduct (the allegedly) merely routine experimentation required to produce these compositions.

In regard to McMaster, the reference teaches the preparation of individual polysaccharide-protein conjugates.

As recognized in the KSR Court that "inventions in most, if not all, instances relay upon building blocks long since uncovered." (*KSR, p.* 15). However, when a combination of elements provides an unpredictable result the invention is not obvious. This is the case here.

Applicant has repeatedly provided evidence of the unpredictability of the vaccine art. The Gizurarson paper was brought to the Examiner's attention to show that vaccinology is often an unpredictable art. This general point is likewise demonstrated in the Lindberg paper discussed above. Applicant's submitted the Gizurarson paper to highlight that one skilled in the art would appreciate that vaccinology is generally unpredictable. The paper shows that even combinations of antigens which might be obvious to try are often not efficacious, only marginally efficacious, and in some instances even produce unexpected deleterious effects. The applicant is conscious of the current claim elements and also of the particulars of the Gizurarson paper.

By way of further example of unpredictability, the applicant respectfully submits a 2005 paper by Buttery *et al.*, published in the Journal of the American Medical Association. (Buttery *et al., Immunogenicity and safety of a Combination Pneumococcal-Meningococcal Vaccine in Infants*, 293(14):1751-1757 (2005)). (Appendix 5). Briefly, the Buttery *et al.* paper looked "To determine the safety and immunogenicity of a combination 9-valent pneumococcal-group C meningococcal conjugate vaccine (Pnc9-MenC) administered as part of the routine UK infant immunization schedule." (Buttery *et al., p.* 1751). In particular, Buttery *et al.* determined that the "Pnc9-MenC combination vaccine administered to infants at ages 2, 3, and 4 months **demonstrated reduced** group C meningococcal immunogenicity compared with MenC vaccine. The immunogenicity of concomitantly administered Hib and DTwP vaccines **was also diminished**. . . . [and that] The **reduced** MenC immunogenicity may limit the development of the Pnc9-Menc vaccine." (Buttery *et al., p.* 1751, emphasis added). In commenting on their research, Buttery *et al.* state "It illustrates the **unpredictability** of immunogenicity when **combining multivalent vaccines, each immunogenic in separate form**. (Buttery *et al., p.* 1754, emphasis added).

One of the problems associated with the use of multivalent conjugate vaccines is that the presence of excessive carrier proteins to which the population has been previously vaccinated results in the failure of the subject to produce an immune response against the polysaccharide

epitope. This was, and remains, a concern in the art. For example, in a paper by Schutze *et al.*, entitled "*Carrier-induced epitopic suppression, a major issue for future synthetic vaccines*," demonstrated that a conjugation of an epitope to a carrier protein to which the organism had already been vaccinated resulted in suppression of the immune response to the epitope. (Schutze *et al.*, J. Immun., 135(4):2319-2322 (1985), at, *p.*2320) (Appendix 6). The paper states, "This study demonstrates clearly that the epitopic suppression could present a major problem for constructing synthetic vaccines. Because most humans have been exposed [tetanus toxoid] the preexisting immunity could prevent the induction of an antibody response against a synthetic epitope conjugated to this carrier." *Id.* at *p.* 2321). In 1998 Renjifo *et al.*, reported the "apparent epitopic suppression in humans" and stated "therefore, prior exposure of the target population to a carrier protein may render this protein unsuitable as a carrier; this phenomenon raise important questions concerning strategies for vaccine development." (See, Renjifo *et al.*, J. Immun. 161:702-706, 704 (1998)) (Appendix 7). As late as 2005 those in the art remained concerned about carrier induced epitope suppression with tetravalent meningococcal A, C, Y, and W-135 conjugate vaccines. (*See*, Baraldo *et al.*, Infect. Immun. 73(9):5835-5841 (2005), *p.* 5839) (Appendix 8). Consequentially, the predictability of the art related to multivalent conjugate vaccines was uncertain. Therefore the probability of technical success of a multivalent polysaccharide-protein conjugate vaccine was highly unpredictable regardless of the suppositions of Lindberg and Levine *et al.*

Additional references can be made available for the Examiner's considerations that speak to the unpredictability in the field of vaccine development.

All of the above (and previously made) remarks notwithstanding, and while in no acquiescing to the Examiner's arguments or conclusion that a *prima facie* case of obviousness has been established, the applicant would like to provide the following additional remarks.

First, the applicant has enjoyed strong increasing commercial success with their tetravalent (A, C, Y, and W-135) meningococcal polysaccharide-diphtheria toxoid conjugate vaccine named MENACTRA®. The MENACTRA® vaccine is the only tetravalent (A, C, Y, and W-135) meningococcal polysaccharide-protein conjugate vaccine licensed in the U.S. It has been licensed in the U.S. since 14 January 2005. The MENACTRA® vaccine posted 2006 First Quarter sales in the U.S. alone of €53,000,000. (Appendix 9, *p.* 2). The commercial success of

the MENACTRA® vaccine in the U.S. and in other world markets, and the absence of any other commercially available tetravalent meningococcal polysaccharide conjugate vaccine underscores the satisfaction of a long felt need for such an important product. While in no way conceding that a *prima facie* case of obviousness has been established, the commercial success of the MENACTRA® vaccine when viewed under the framework set forth by the U.S. Supreme Court in the landmark *Graham v. John Deere Co.*, decision strongly points to the non-obviousness of the presently invention. (*Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966)).

Second, should the Examiner find it helpful the applicant is able to provide evidence of invention prior to the effective dates of the various references cited by the Examiner.

In view of the remarks previously made of record and those presented herein, the applicant must respectfully submit that the Examiner has not established the *prima facie* obviousness of the pending claims. The pending obviousness rejections should be withdrawn without further delay or prejudice to the applicant's interests.

After discussing the above-mentioned references, the Examiner states:

> **That no deleterious side effects** or **suppression of immunogenicity was expected** by those skilled in the art and that a reasonable expectation of success of such a combined conjugate vaccine was anticipated by those skilled in the art at the time of invention ism [sic] evident from Levine et al. going to the extent of performing a cost-effectiveness analysis for routine immunization with a quadrivalent . . . , and Lindberg predicting the potential **marketing** . . . glycoconjugates.

(Final Office Action, ¶ 27, emphasis added). The applicant was unable to identify the "**deleterious side effects**" or "**suppression of immunogenicity**" said to appear in any of the cited references. The Examiner is respectfully asked to provide the citations where these phrases appear in the cited references.

Finally, applicant respectfully submits that he has traversed all grounds of rejection set forth in the Final Office Action. Applicant requests withdrawal of the pending obviousness rejections and movement of the case to allowance without further delay.

Rejection: 10 The Objection to Claim 35

Claim 35 stands objected to for reciting brackets therein. (Final Office Action ¶ 33). The applicant respectfully notes that the brackets formerly recited in claim 35 were as found in the actual chemical names for the compositions. Nonetheless, the above-mentioned amendments to claim 35 removed the brackets from the pending claim. This rejection is thus moot.

Should the examiner have any questions concerning this application, please contact the undersigned.

Respectfully submitted,

Date: 20 SEPT 2007 By: _____

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